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Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* in children

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Background. **Community-acquired, methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is an established pathogen in several areas of the United States, but experience with clindamycin for the treatment of invasive MRSA infections is limited. We compared the outcome of therapy for MRSA with that of methicillin-susceptible (MSSA) invasive infections in children treated with clindamycin, vancomycin or beta-lactam antibiotics.**

Methods. **The demographics, hospital course and outcome of children at Texas Children's Hospital between February and November 2000 and between August 2001 and August 2002 with invasive *S. aureus* infections were reviewed from medical records in this retrospective study.**

Results. **CA-MRSA and community-acquired methicillin-susceptible *S. aureus* (MSSA) caused invasive infections in 46 and 53 children, respectively. The median ages (range) of the children were: MRSA, 3.5 years (2 months to 18.6 years); MSSA, 4.8 years (3 months to 19.8 years). The sites of infection for MRSA *vs.* MSSA isolates, respectively, were: bacteremia, 3 *vs.* 6; osteomyelitis, 14 *vs.* 14; septic arthritis, 5 *vs.* 7; pneumonia, 11 *vs.* 3; lymphadenitis, 7 *vs.* 14; other, 5 *vs.* 8. Among MRSA patients 39 (20 received clindamycin only, 18 had vancomycin initially and 8 were treated with a beta-lactam initially) received clindamycin and 6 received vancomycin as primary therapy. Among MSSA patients, clindamycin, nafcillin or other beta-lactam antibiotics were used in 24, 18 and 9, respectively. The median number of febrile days was 3 (0 to 14) and 2 (0 to 6) for MRSA and MSSA patients, respectively ($P = 0.07$). The median number of days with positive blood cultures was 2 for the MRSA ($n = 16$) and 1 for the MSSA ($n = 18$) patients ($P = 0.04$).**

Conclusion. **Clindamycin was effective in treating children with invasive infections caused by susceptible CA-MRSA isolates.**

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* is an established pathogen in the community (CA-MRSA) in several areas.[1–8] The frequency of resistance to methicillin in *S. aureus,* isolated from children with community-acquired infections seen at Texas Children's Hospital (TCH) increased from 35% in February 2000 to 67% by January 2002.[9] Although the clinical spectrum of infections caused by CA-MRSA resembles those caused by community-acquired methicillin-susceptible *S. aureus* (CA-MSSA) in that skin and soft tissue infections predominate,[2, 6, 7] increasing numbers of children with invasive infection caused by CA-MRSA are being treated.[9, 10]

The antibiotic susceptibility of MRSA isolates from patients with community-acquired infection differs from those of MRSA isolates from patients with nosocomial infections. CA-MRSA isolates typically are susceptible to clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX) and gentamicin, whereas nosocomial isolates are frequently resistant to these antibiotics.[1–10] Clindamycin has been used successfully for many years for treating serious infections caused by methicillin-susceptible *S. aureus* isolates, but clindamycin has not been recommended for the treatment of invasive infection caused by nosocomial MRSA because most strains are resistant.[11]

As a result of the high rate of methicillin resistance among community-acquired *S. aureus* isolates at TCH, guidelines for the use of clindamycin and vancomycin (life-threatening infections), as initial empiric therapy

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for serious infections possibly caused by *S. aureus*, were recommended to the hospital staff in September 2000. In this study we compared the outcome of therapy for CA-MRSA *vs.* CA-MSSA infections in children treated with clindamycin, vancomycin or beta-lactam antibiotics.

METHODS

From February to November 2000 and from August 2001 to August 2002, the Infectious Disease Laboratory at Texas Children's Hospital collected all *S. aureus* strains, isolated by the hospital clinical microbiology laboratory, from children with community-acquired infections at TCH. A research nurse recorded clinical and antibiotic susceptibility information on a standardized form. Bacteremia, pneumonia, septic arthritis, osteomyelitis, pyomyositis, deep abscesses, bursitis and lymphadenitis were considered as invasive infections, and patient's medical records were reviewed. Only patients with community-acquired *S. aureus* infection were included in this study. Community-acquired infection was defined as isolation of *S. aureus* within 72 h of hospitalization or after 72 h, but clinical evidence suggested that it was community-acquired (e.g. bone cultures from surgery done 4 days after admission). Patients with an underlying illness predisposing to frequent hospitalization such as immunodeficiency, cystic fibrosis, chronic renal failure or history of malignancy were excluded. Although no hospitalizations were documented in patients with other underlying conditions such as asthma or chronic skin illness, they had histories of frequent visits to medical facilities. Thus for these patients it could be more appropriate to consider their infections as "presumably" community-acquired. From the medical records we obtained demographic and clinical information (dates of admission and discharge, clinical course, hospital days, intensive care unit days, febrile days ($\geq$100.4ºF), days of positive blood cultures in patients with bacteremia, surgical treatment, underlying medical conditions and outcome). We also obtained information pertaining to antibiotic therapy (initial and final antibiotic, dose and duration of treatment). The Institutional Review Board of Baylor College of Medicine approved the study.

Laboratory methods. Isolates were identified as *S. aureus* by the clinical laboratory according to standard methods.[12] Screening for methicillin resistance was performed by disk diffusion with a 1-μg oxacillin disk and by growth on Mueller-Hinton agar containing 4% NaCl and oxacillin (6 μg/ml), after an incubation period of 24 h at 35°C, using National Committee for Clinical Laboratory Standards (NCCLS) methodology.[13, 14] Antibiotic susceptibility was performed by the disk diffusion method according to the NCCLS guidelines. The antibiotics tested included vancomycin, clindamycin, TMP-SMX, erythromycin, gentamicin and penicillin. Results were determined after 24 h of incubation at 35°C according to NCCLS breakpoints.[14]

For all isolates that were erythromycin-resistant and clindamycin-susceptible, detection of the presence of inducible macrolide-lincosamide-streptogramin B (MLS_B) resistance was performed by disk diffusion with the use of clindamycin and erythromycin disks set 15 to 20 mm apart. Zone shapes were read after a 24-h incubation period at 35°C. A flattened or blunted ("D-shaped") zone of inhibition around the clindamycin disk on the side facing the erythromycin disk indicated an inducible MLS_B-resistant phenotype,[16] and the isolate was considered resistant to clindamycin. If the entire zone of inhibition surrounding the clindamycin disk was round, the mechanism of resistance was assumed to be active efflux for macrolides and the organism was considered susceptible to clindamycin.[17, 18]

Statistical analysis. To compare differences between groups, the Mann-Whitney *U* test was used for continuous variables without normal distribution; The chi square test was used for dichotomous variables. All analyses were two tailed, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS for Windows software Version 10.0.

RESULTS

During the study periods community-acquired *S. aureus* or presumably community-acquired was isolated from 99 patients with deep-seated infections; 53 were MSSA and 46 were MRSA. With the exception that CA-MSSA infection occurred more frequently in Hispanic children, no significant differences were found in demographic or clinical characteristics between CA-MRSA and CA-MSSA infection in children with invasive infection (Table 1). The site of infection between groups was similar, except pneumonia was more frequent in the MRSA group than in the MSSA group ($P = 0.001$) (Table 2). Among patients with pneumonia 11 had empyema or underwent surgical drainage and were considered to have complicated pneumonia. Three patients with MRSA and 6 patients with MSSA infections had bacteremia without other identified sites of infection. *S. aureus* was also isolated from blood in 13 (11 with bone and joint infections) and 12 (9 with bone and joint infections) patients of the MRSA and MSSA groups, respectively.

Virtually all of the CA-MRSA and CA-MSSA isolates from children with invasive infections were susceptible to gentamicin, vancomycin, TMP-SMX and clindamycin. All but three strains in the MSSA group were penicillin-resistant. Among the MRSA isolates 83% were resistant to erythromycin, whereas only 17% were resistant to erythromycin in the MSSA group ($P = 0.0001$). All erythromycin-resistant and clindamycin-susceptible isolates were tested for inducible clindamycin resistance by

TABLE 1. Demographic and clinical characteristics of patients with community-acquired MRSA and MSSA invasive infections at Texas Children's Hospital

Variable	MRSA (n = 46)	MSSA (n = 53)	P
Age (mean ± SD) in yr	5.0 ± 4.7	7.2 ± 5.8	
Median (range)	3.5 (2 mo–18.6 yr)	4.8 (3 mo–19.8 yr)	NS
Gender male	28	28	NS
Race			
African-American	24	21	0.0001
White	11	5	
Hispanic	11	23	
Asian		2	
Other		2	
Underlying conditions			
Asthma	2	2	NS
Chronic skin illness*	3	3	
Malignancy†	1	1	
Autoimmune diseases		1	
Other	2	1	
Surgical interventions			
Yes	40 (87.0%)	38 (75.0%)	NS
No	6 (13.0%)	15 (25.0%)	

* Eczema (5 of 6)

† Had *Staphylococus aureus* infection at clinical presentation before diagnosis of the malignancy.

TABLE 2. Site of infection in patients with community-acquired MRSA and MSSA invasive infections

Site of Infection	MRSA (n = 46)	MSSA (n = 53)	P
Bacteremia	3	6	
Osteomyelitis*	14 (9)†	14 (5)	
Septic arthritis	5 (2)	7 (4)	
Complicated pneumonia‡	11 (1)	3 (1)	0.001
Lymphadenitis	7	14	
Deep abscesses§	1	2	
Pyomyositis	2 (1)	4 (2)	
Mastoiditis		1	
Bursitis	2	1	

* Five patients also had myositis as documented by MRI studies.

† Numbers in parentheses, number of patients with positive blood cultures.

‡ All but one patient had complicated pneumonia: empyema (11); lung abscess (2). In one patient the diagnosis was established by sputum culture.

§ Cerebral, paraspinous, psoas.

the D test. Although 38 of 46 (83%) MRSA isolates were erythromycin-resistant, the inducible MLS_B-resistant phenotype was found in only 1 (2.2%) of the strains. The other clindamycin-resistant MRSA isolate had the constitutive MLS_B-resistant phenotype.

The antibiotics administered are outlined in Table 3. Twenty children in the MRSA group and 18 in the MSSA group, respectively, received clindamycin as their only effective antistaphylococcal therapy. The difference in the number of children between initial and final antibiotic in each group is a consequence of changing the empiric initial therapy for median of 3 days (range, 1 to 11) to a definitive antibiotic on the basis of antibiotic susceptibility pattern. The reasons for continuing vancomycin therapy were: clindamycin resistance (2); persistent positive blood cultures (2); suspicion of endocarditis (1); and reason not documented (1).

TABLE 3. Antibiotics used for the treatment of CA-MRSA and CA-MSSA invasive infections

Antibiotics	MRSA (n = 46)		MSSA (n = 52)	
	Initial	Final	Initial	Final
Clindamycin*	20	39	18	24
Nafcillin	5	0	16	18
Vancomycin†	18	6	15	0
Other β-lactam antibiotics‡	3	0	3	9
TMP-SMX	0	1	0	1

* In 9 patients combined with gentamicin or cefotaxime; 4 in the MRSA and 5 in the MSSA.

† Usually combined with nafcillin or other β-lactams.

‡ Cephalosporins, ticarcillin/clavulanic acid.

In 35 (90%) of 39 patients treated with clindamycin as the final antibiotic in the MRSA group, a surgical procedure (incision, aspiration, drainage or debridement) was performed as part of their treatment. These procedures were performed in all patients with complicated pneumonia, lymphadenitis, septic arthritis, bursitis and pyomyositis and in 11 of 13 patients with osteomyelitis. Two children with bacteremia did not require a surgical procedure. In the MSSA group 19 (79%) of 24 patients who received clindamycin as their final antibiotic had a surgical procedure. All patients with lymphadenitis, septic arthritis, pyomyositis, bursitis and deep-seated abscesses had a surgical intervention. No surgical intervention was performed in 2 of 4 patients with osteomyelitis, 1 of 3 with complicated pneumonia and 2 children with bacteremia.

In 38 (20 MRSA and 18 MSSA) children who received clindamycin as their only effective initial and final antistaphylococcal antibiotic, the percentage of surgical procedures performed was similar, 80 and 78% in the MRSA and MSSA groups, respectively. Table 4 shows the number of patients who had a surgical intervention according to the sites of infection. A surgical procedure was performed in 83% of those patients who received vancomycin as their final antibiotic; a similar percentage was found in children treated with nafcillin.

The dose and duration of clindamycin treatment varied with the diagnosis. For patients with lymphadenitis the median dosage was 31 mg/kg/day divided every 8 h (range, 30 to 40 mg/kg/day) and clindamycin was given for a median of 14 days (range, 4 to 15 days). Usually these patients received 2 to 4 days of intravenous antibiotic treatment and were discharged to receive oral therapy. In patients with bacteremia, complicated pneumonia and musculoskeletal infections, the clindamycin dose was 40 mg/kg/day and was administered for a median of 20 days (range, 10 to 56 days), primarily by the intravenous route.

The number of days with blood cultures positive in patients with bacteremia was greater in children with MRSA infection than in the MSSA group (median, 2 *vs.* 1; $P = 0.04$) (Table 5). Similarly the number of hospital days

TABLE 4. Site of infection and surgical treatment in patients with invasive infection treated with clindamycin as the only antibiotic

Site of Infection	Total (n = 20)	MRSA Surgical Treatment		Total (n = 18)	MSSA Surgical Treatment	
		Yes (n = 16) 80%	No (n = 4) 20%		Yes (n = 14) 78%	No (n = 4) 22%
Bacteremia	2	0	2	2	0	2
Lymphadenitis	5	5	0	9	9	0
Complicated pneumonia	1	1	0	1	0	1
Osteomyelitis	7	5	2	5	4	1
Septic arthritis	3	3	0	1	1	0
Bursitis	2	2	0	0	0	0

TABLE 5. Hospital course and outcome of children with invasive CA-MRSA and CA-MSSA infection

Outcome	MRSA (n = 46)	MSSA (n = 53)	P
Cure/improvement	45	52	NS
Death	1	1	
Febrile days			
Mean ± SD	3.93 ± 4.12	1.81 ± 1.69	0.07
Median	3 (0–14)*	2 (0–6)	
Hospital days			
Mean ± SD	12.02 ± 7.64	9.02 ± 8.54	0.005
Median	9 (3–37)	7 (0–44)	
PICU days	n = 8	n = 3	
Mean ± SD	6.50 ± 4.75	9 ± 4.36	0.49
Median	9 (1–15)	7 (6–14)	
Days of BC+	n = 16	n = 18	
Mean ± SD	3.38 ± 2.45	1.50 ± 1.04	0.04
Median	2 (1–11)	1 (1–4)	
Days of BC+†	n = 15	n = 18	
Mean ± SD	2.87 ± 2.45	1.50 ± 1.04	0.084
Median	1 (1–8)	1 (1–4)	

† Excluding one patient with 11 days of positive cultures (see text).
* Numbers in parentheses, range.
PICU, pediatric intensive care unit; BC+, blood culture-positive.

was significantly greater in the MRSA group (median, 9 *vs.* 7; P = 0.005). Although not statistically significant (P = 0.07), the duration of febrile days was also greater in children in the MRSA group than in the MSSA group. Excluding a patient with osteomyelitis and myositis who required drainage several times and had positive blood cultures for 11 days, the number of days with blood cultures positive in patients with bacteremia was similar in both groups (median, 1 *vs.* 1; P = 0.08). When we compared the number of days with blood cultures positive based on the initial effective antibiotics (clindamycin n = 10 *vs.* vancomycin n = 13), no significant difference was found (median, 1 *vs.* 1; P = 0.2).

All treated patients in each group were cured or had a significant improvement at the time of discharge from the hospital. One patient in each group died. The patient who died in the MRSA group had pneumonia and hepatosplenomegaly at the time of admission. T cell lymphoma was diagnosed; a blood culture grew MRSA, and the child was treated with vancomycin. Subsequent blood cultures were negative. The patient died 2 weeks later. Vancomycin-resistant *Enterococcus faecium* was isolated from blood culture, and *Candida albicans* was isolated from lung tissue. A patient in the MSSA group died before antimicrobial therapy was initiated.

DISCUSSION

The emergence of community-acquired methicillin-resistant *S. aureus* causing serious infections in children has modified our initial empiric therapy for systemic infections possibly caused by these organisms.[9] MRSA clones circulating in the community have antibiotic susceptibility profiles that differ from that of nosocomial MRSA infections. *In vitro* CA-MRSA isolates usually are susceptible to vancomycin, clindamycin, TMP-SMX and gentamicin.[2, 9, 19] Oral clindamycin or TMP-SMX has been recommended as initial empiric therapy for non-critically ill patients in areas where CA-MRSA isolates are found.[19] For children who are critically ill, empiric therapy with intravenous clindamycin or vancomycin in combination with third generation cephalosporin has been suggested.[3, 9] However, information about clindamycin treatment of serious infections caused by CA-MRSA is limited. Frank et al.[10] reported satisfactory improvement or cure in a small group of children with invasive infections treated with clindamycin and surgical drainage. In our study we found that clindamycin was effective in the treatment of invasive infection in both MRSA and MSSA groups. All patients were cured or had a substantial improvement at the time of discharge. A surgical procedure was performed in a high percentage of the patients. In ~50% of the patients who had received clindamycin as final therapy, the treatment was started with other antibiotics before changing to clindamycin. Thus one can question whether the satisfactory final outcome of these patients was primarily the result of the combination of an adequate surgical treatment and the antibacterial effect of the initial antibiotic for a median of 4 days *vs.* the completion of treatment with clindamycin. However, similar results were observed when we examined the children who received clindamycin as their only effective initial and final antistaphylococcal therapy.

Two major concerns when using empiric clindamycin as therapy of serious infections potentially caused by *S. aureus* are the proportion of clindamycin-resistant

strains circulating in a specific community and the development of resistance during the treatment with clindamycin. The rates of clindamycin resistance among CA-MRSA isolates in different communities vary. In our hospital virtually all of the community-acquired and presumably community-acquired MRSA and MSSA have been susceptible to clindamycin, supporting its use as empiric treatment in children with infections possibly caused by *S. aureus.* In South Texas 94% of CA-MRSA isolates from children without risk factors were susceptible to clindamycin.[20] However, other regions of the United States report clindamycin resistance in ≥25% of CA-MRSA isolates.[21, 22] Regional patterns of antibiotic use, genetic modification among clones circulating in the community or differences in the definition of community-acquired infections are among the many factors that may cause these variations and deserve further evaluation.

In 1969 McGehee et al.[23] reported the development of resistance to lincosamides during the treatment of patients with erythromycin-resistant *S. aureus* infections. It is now known that modification of an adenine residue of bacterial 23S ribosomal RNA is the primary mechanism of acquired resistance to macrolide, lincosamide and streptogramin B (MLS_B) antibiotics and confers cross-resistance to these antibiotics. Expression of MLS_B resistance in staphylococci is either constitutive or inducible. When it is constitutively expressed, resistance to all MLS antibiotics is present. When MLS_B is of the inducible form, bacteria are resistant to macrolides but appear susceptible to lincosamides and streptogramin B antibiotics with the use of standard susceptibility techniques.[24] In our hospital all erythromycin-resistant *S. aureus* isolates are tested for the presence of the inducible phenotype (MLS_B) by the D test. Despite a high frequency of erythromycin-resistant isolates in the MRSA group, the inducible phenotype was found in only one isolate. This finding contrasts with the high frequency (67, 84 and 93%) of inducible clindamycin resistance reported by investigators from New York, Minnesota and Chicago.[25–27]

Frank et al.[27] pointed out the risk of clinical failure associated with the development of clindamycin resistance in children with CA-MRSA. They also evaluated the responses to clindamycin in children with both erythromycin-susceptible and erythromycin-resistant *S. aureus* infections. All nine children with erythromycin-susceptible strains had good responses when treated with clindamycin.[10] Among nine children with erythromycin-resistant, D test-positive isolates treated with clindamycin, there was documented clinical failure and development of resistance to this drug in a child with complicated pneumonia. The remaining children had a good response to therapy with clindamycin.[27] These findings have suggested that clindamycin is an alternative for the therapy of CA-MRSA if the inducible resistance phenotype can be identified shortly after empiric treatment is started. In the setting of serious infections, the clindamycin should be discontinued if this phenotype is found.

The distribution of clinical sites of invasive infection associated with CA-MRSA was similar to that associated with CA-MSSA with the exception of complicated pneumonia which was significantly more frequent in the MRSA group. Recently it has been suggested that a particular combination of the Panton-Valentine leukocidin determinant (PVL), which encodes a virulence factor for primary skin infections and pneumonia, and the *mecA* gene has created a superadapted *S. aureus* strain in the community.[28] PVL has been associated with highly lethal necrotizing pneumonia in young immunocompetent patients.[29] Our pneumonia strains are being evaluated for the PVL gene.

Information about the clinical course of patients with CA-MRSA invasive infections is very limited. We found that children with invasive CA-MRSA infections were hospitalized longer than children with invasive infections caused by CA-MSSA isolates. Although longer hospitalization in the MRSA group may be associated with the longer duration of fever in this group (although not statistically significant), it is also possible that physicians were more concerned about documenting appropriate treatment for infections caused by MRSA than by MSSA before discharging their patients. Although surgical interventions are crucial for the resolution of deep-seated and complicated infections and more than one procedure is often required to completely remove infection foci, the finding that there was no difference between the number of days with blood cultures positive with respect to the initial effective antibiotic suggests that clindamycin is as efficient as vancomycin in sterilizing the blood of *S. aureus.*

Our findings support the use of clindamycin as an alternative for empiric and final treatment of children with CA-MRSA when the isolate is fully susceptible to clindamycin. Prospective surveillance of resistance to clindamycin and testing for presence of the inducible resistance phenotype in erythromycin-resistant staphylococci should be performed by clinical microbiology laboratories to avoid therapeutic failures as a consequence of constitutive expression of resistance during therapy with clindamycin by isolates with this phenotype. In our study all children in the MSSA group who received clindamycin as initial empiric treatment were continued on the same therapy. Other children were changed from vancomycin to clindamycin rather than a beta-lactam antibiotic when the isolate was methicillin-susceptible. We must discourage the use of clindamycin in patients with MSSA infection in whom a beta-lactam antibiotic is a more appropriate option. As noted by several authors,[3, 9, 28] in the normal host with superficial *S. aureus* infection, the role of antibiotic therapy for resolution of infection is probably not as critical as it is for invasive infections. In patients

with superficial infection caused by CA-MRSA who have adequate clinical response despite the treatment with an antibiotic to which the organism was not susceptible, modifying antibiotic treatment is not as crucial as it is for invasive infections. As with any antibiotic, the judicious use of clindamycin is critical to minimize the potential for clindamycin resistance to become more frequent among *S. aureus* isolates in the community. These points must be addressed during the implementation of guidelines for the treatment of CA-MRSA infections. If clindamycin resistance is already at levels that exceed 10 to 15% of CA-MRSA isolates or becomes this high, clindamycin use for empiric therapy of serious but non-life-threatening infections potentially caused by *S. aureus* will be diminished. Vancomycin would remain the primary empiric agent in this setting although alternative antibiotics include linezolid or possibly TMP-SMX.

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